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In Re Application of: Olivier NECKEBROCK, et al.

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For: PROCESS FOR THE PREPARATION OF AND CRYSTALLINE FORMS OF OPTICAL ENANTIOMERS OF MODAFINIL

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF MATTHEW L. PETERSON, PHD.

I, Matthew L. Peterson, Ph.D. hereby declare the following:

(1) I received a Bachelor of Science in Chemistry from Purdue University in 1992, and a Ph.D. in Chemistry from Carnegie Mellon University in 1999. From January 2004 to the present, I have served as a Senior Scientist and Group Leader in Pharmaceutical Chemistry at TransForm Pharmaceuticals, Inc., 29 Hartwell Avenue, Lexington, MA 02421. A copy of my current *curriculum vitae* is attached hereto as Exhibit 1.

(2) MODAFINIL is the active ingredient in a commercial pharmaceutical product made by Cephalon Inc. (PA, USA). It exists in (-) and (+) isomeric forms and as a racemic mixture.

(3) TransForm Pharmaceuticals, Inc. has conducted research into various solid forms of (-)-MODAFINIL. In the process of conducting this research, we have recrystallized the (-) enantiomer of modafinil from ethanol under various conditions, as reported in paragraphs (4) to (8), *infra*. These experiments were performed under my direction and control.

(4) 29.0 mg (0.106 mmols) of (-)-MODAFINIL and 800 µl of ethanol were placed in an HPLC vial. The vial was crimp sealed, the sample was heated with a heat gun until the solids dissolved, and the septum was punctured with a needle. The sample was allowed to stand at room temperature overnight. No solids were observed in the morning. The solvent

was evaporated and the resulting solids were analyzed by powder X-ray diffraction (PXRD) and found to be the polymorph we designate as Form E (-)-MODAFINIL. A PXRD pattern of Form E of the (-) enantiomer of MODAFINIL is attached hereto as Exhibit 2.

(5) 30.1 mg (0.110 mmol) of (-)-MODAFINIL and 200 µl of ethanol were heated to 75°C and held there. After about 30 minutes some of the solids remained undissolved. An additional 200 µl of ethanol was added, and the mixture again heated to 75° C and held there. The sample was nearly dissolved. The sample was held for about another 2 hours, then cooled to 5°C at a rate of about 1°C/minute. The sample was held at 5°C for about 90 minutes, then removed from the cooling station and allowed to stand at room temperature for about 30 minutes. The sample was then dried under nitrogen and analyzed by PXRD. The sample was found to be the polymorph we designate as Form E (-)-MODAFINIL.

(6) 105.9 mg (0.3874 mmol) of (-)-MODAFINIL was slurried in 1.5 ml of ethanol. The sample was allowed to stir over the weekend at room temperature. 400 µl of the slurry was removed from the vial and centrifuge filtered. The filter cake was removed from the vial, analyzed by PXRD, and found to be the polymorph we designate as Form E (-)-MODAFINIL. Another 600 µl of the slurry was removed from the vial and centrifuge filtered. This filtrate was dried under flowing nitrogen gas. The resulting solids were analyzed by PXRD and found to be the polymorph we designate as Form D (-)-MODAFINIL. A PXRD pattern of Form D of the (-) enantiomer of MODAFINIL is attached hereto as Exhibit 3.

(7) 449.2 mg (1.643 mmols) (-)-MODAFINIL and 20.2 mg (0.074 mmols) racemic modafinil were dissolved in 5.0 ml of methanol and aliquoted into 5 vials, at 1.0 ml/vial. The methanol was allowed to evaporated, leaving behind a solid material containing (-)-MODAFINIL of about 98% purity. About 3 ml of ethanol was added to one of the vials. The sample was warmed to dissolve the material and cooled to room temperature. No solids were observed. The sample was cooled to 0°C, where solids were observed. The solids were isolated by filtration and dried. The sample was left overnight. The next day, the sample was analyzed by PXRD and found to be the polymorph we designate as Form D (-)-MODAFINIL.

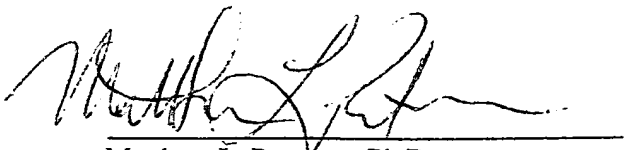
(8) About 70 mg para-toluenesulfonic acid monohydrate was added to a solution of 15.8 grams (-)-benzhydrylsulfinylacetic acid in 150 ml methanol. The reaction was stirred

at reflux for two hours, cooled to room temperature, and stirred overnight at room temperature to produce a solution of (-)-benzhydrylsulfinyl methyl ester. 75 ml of this solution was taken up and transferred to a 3-necked round bottom flask equipped with a condenser and a magnetic stir bar. 50 ml of methanol were added, and anhydrous ammonia was bubbled through the reaction mixture for 10 minutes. A precipitate began to form, and was collected using a Hirsh funnel to give a solid (422 mg) which was characterized by NMR as a side product. The filtrate was then acidified using HCl and concentrated under vacuum to give a solid with was purified using column chromatography, using 3:1 mixture of ethyl acetate:hexane as the eluant. The filtrates from the column were then combined and concentrated *in vacuo* to (-)-MODAFINIL as a colorless solid (590 mg). PXRD analysis was performed on this solid, and it was determined to be the polymorph we designate as Form D (-)-MODAFINIL. This solid was then dissolved in about 3 ml ethanol by heating to boiling with a heat gun. The sample was allowed to cool on the bench top. Crystallization was observed at room temperature. The crystals were isolated by filtration on a Büchner funnel and allowed to air dry on the filter. The crystals were characterized by PXRD and found to be the polymorph we designate as Form E (-)-MODAFINIL.

(9) Based on the experiments described in paragraphs 4 to 8, *supra*, I conclude that recrystallization of (-)-MODAFINIL from ethanol under varying conditions may result in formation of more than one polymorph form of the compound. In my experience, and based on the data herein, different polymorphic forms of the compound may be produced, depending upon the conditions under which the recrystallization is performed.

(10) I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further, that the statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: 01-June-2006



Matthew L. Peterson, Ph.D.

EXHIBIT 1

Matthew Lynn Peterson

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Hopkinton, MA 01748
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Experience

TransForm Pharmaceuticals, Inc.

Senior Scientist – Group Leader, Pharmaceutical Chemistry (January 2004 – present)
Managed a group of 6 people including 3 Ph. D., 1 M. S. and 2 B. S. level scientists. Interfaced with engineering and software development groups to develop an automated crystallization platform that was deployed to several off-site research groups. Interfaced with discovery groups on lead optimization focusing on the importance of physical properties of the compounds being advanced. Lead project teams through form evaluation and characterization, excipient compatibility, formulation design, crystallization scale up and in vitro and in vivo testing. Headed and expanded a research collaboration with the University of South Florida focused on pharmaceutical co-crystals and solvent sparing synthetic methods. Continued to lead the internal publications efforts. Member of Science and Technology Organization and Research Management team.

Senior Scientist in Pharmaceutical Research (January 2003 – January 2004)
Identified and carried out physico-chemical evaluation of several compounds for internal drug development program. Evaluated the pharmacokinetic and pharmacodynamic performance of development compounds using animal studies. As part of a product research program formulated strategy for development and/or outsourcing of new drug candidates. Headed research collaboration with an academic research group at The University of South Florida focused on the development of new methods for the modification of the physical performance of pharmaceutical compounds by modification of their solid form. Managed several interns, one MS level assistant scientist and one Ph. D. level scientist. Lead internal publication efforts. Provided training for proper laboratory notebook practices to new scientific staff. Sourced compounds for exploratory studies for internal drug development efforts.

Scientist in Solid State Chemistry and Targeted Discovery (August 2001 – January 2003)
Studied polymorphism, hydrates, solvates and salts of pharmaceutical compounds using traditional high-throughput crystallization techniques. Developed novel process upgrades to TransForm's high-throughput crystallization platform. Developed crystallization screen focused on inhibition of calcium oxalate crystal growth. Supervised multidisciplinary team responsible for development of automated experimentation platforms. Managed outsourcing of single crystal X-ray structure determination. Acted as the contact person and led internal scientific efforts for several projects with outside partners. Managed several interns, one MS level assistant scientist and one Ph. D. level scientist. Lead internal publication efforts. Provided training for proper laboratory notebook practices to new scientific staff. Sourced compounds for exploratory studies for internal drug development efforts.

Kansas State University, Manhattan, KS (October 1999 – August 2001).
Postdoctoral research with Prof. Mark D. Hollingsworth
Studying the ferroelastic and ferroelectric properties of urea and thiourea inclusion crystals and 4-tert-butlycalix[4]arene clatharates. Synthesized and characterized organic, organometallic and isotopically labeled compounds. Determined the single crystal structures of these often disordered and/or twinned crystals using X-ray diffraction techniques. Optimized crystal growth

conditions to yield centimeter sized crystals for X-ray topography. Installed and maintained a 300 MHz NMR used for solid state magic angle spinning experiments. Assisted in the design of novel instrumentation used to study ferroelasticity and ferroelectricity at high and low temperatures by optical microscopy.

Carnegie Mellon University, Pittsburgh, PA (July, 1993 – October, 1999)
Ph. D. with Prof. Stuart W. Staley
Focused on molecular structure and dynamic molecular processes in the solid and liquid state. Synthesized and characterized the compounds utilized in these studies. Measured dynamic molecular process using NMR methods, including full line shape analysis and saturation transfer. Determined single crystal structures using X-ray diffraction techniques. Maintained, administered and upgraded the group's GE 300 MHz NMR. Organized departmental graduate student seminar series. Departmental teaching assistant of the year, 1996. Teaching assistant 1993 - 1999.

University of Umeå, Umeå, Sweden (July-Aug. 1997; June-July 1998)
Research assistant, advisor: Professor Bertil Eliasson
Part of a collaborative research program involving the determination of rate constants for the dynamic processes of bridged dicyclooctatetraenes and their dianionic salts by dynamic NMR spectroscopy. Worked with a Bruker 360 MHz NMR spectrometer.

Purdue Univeristy, West Lafayette, IN (December, 1991 – June, 1993)
Undergraduate research with Prof. Bart Kahr
Grew and optically characterized mixed crystals of sodium chlorate / sodium bromate and lead nitrate / barium nitrate. Grew organic dye inclusion crystals (inorganic crystals with organic dye inclusions). Organized and maintained a crystal library.

Education

Carnegie Mellon University, Pittsburgh, PA
Ph. D. Chemistry October, 1999

Purdue University, West Lafayette, IN
B.S. Chemistry December, 1992

Instrumentation and Computer Programs

Single crystal and powder x-ray diffraction, Raman Spectroscopy, ^{1}H and ^{13}C variable temperature NMR, Spin-Saturation Transfer (SST), IR, UV-VIS, polarized light microscopy, thermal microscopy, analytical and preparative HPLC, GC, DSC, TGA. TGA-IR, ultrafast video microscopy, Synchrotron White Beam X-ray Topography, NLO microscopy, CP/MAS NMR, GC/mass spectroscopy,. Gaussian92, Gaussian94W, Gaussian98W and Gaussian03W, the Cambridge Structural Database, Materials Studio and Cerius2 packages of programs, Shelx, SMART, SAINT, CrystalStructure and Sir93 crystals structure determination and refinement software, gNMR, Microsoft Word, Excel, PowerPoint, Outlook, Adobe Photoshop and Premier.

Experimental Techniques

High-throughput combinatorial crystallization. High-throughput chemical library screening. Experienced in multi-step and microscale synthesis of organic compounds utilizing anhydrous, oxygen free and low temperature techniques. Practiced in dynamic, 1D and 2D NMR techniques used for characterization of organic compounds and determination of rate constants of dynamic molecular processes. Determination of single crystal x-ray structures by direct methods using both serial and area detectors. Optimization of molecular structures, calculation of energy barriers and electron distributions using semi-empirical, molecular mechanics and *ab initio*

methods. Controlled crystal growth and habit modification. Synchrotron Whitebeam X-ray Topography. Single crystal ferroelastic and ferroelectric experiments.

Patents

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Topiramate Sodium Trihydrate. PCT/US03/04357 filed 2/14/2002.
Topiramate Salts and Compositions Comprising them. 10/295,995 filed 11/28/2002.
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Pharmaceutical Compositions with Improved Dissolution. 10/601,092 filed 6/20/2003.
Pharmaceutical Compositions with Improved Solubility. PCT/US03/19574 filed 6/20/2003.
Crystalline Salts of Celecoxib. 11/25/2003.
Pharmaceutical Co-crystal Composition. 60/451,213 filed 2/28/2003.
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Mixed co-crystals and pharmaceutical compositions. US 2005267209, 53 pp.
Preparation of organic acid salts of gabapentin. WO 2004091278

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Vishweshwar, Peddy; McMahon, Jennifer A.; Peterson, Matthew L.; Hickey, Magali B.; Shattock, Tanise R.; Zaworotko, Michael J. Crystal engineering of pharmaceutical co-crystals from polymorphic active pharmaceutical ingredients. Chem Commun (Cambridge, United Kingdom) **2005**, (36), 4601-4603.

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Lectures and Posters

ICCOSS talk

ACA talk

High-Throughput Polymorphism Studies on Acetaminophen and an Experimental Analysis of the Metastable Form III. American Chemical Society Lecture. August, **2002**.

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Tailor-Made Impurity Control of Elastic Versus Plastic Domain Switching in Ferrolastic Inclusion Compounds. Lecture, Midwest Solid State Organic Chemistry Conference, June, **2000**.

Structural Effects of C6 Substitution in 6-(4-(Dimethylamino)phenyl)fulvenes. Midwest Solid State Organic Chemistry Conference, **1999**.

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Electronic Effects of *para*-Substitution on the Molecular Structures of 6-Aryl-6-methylfulvenes. American Chemical Society Lecture, **1994**.

EXHIBIT 2

PXRD of (-)-MODAFINIL Form E:

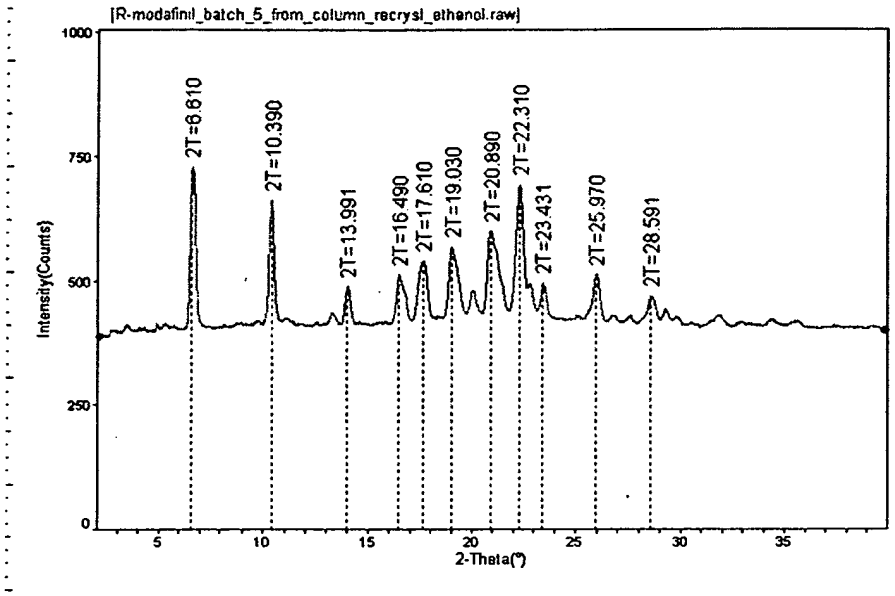

EXHIBIT 3

PXRD of (-)-MODAFINIL Form D: